references does **not** teach or suggest the use of an isolated endothelial progenitor cell in the treatment of ischemia or for treating a blood vessel injury.

Noishike, et al., **seeded** bone marrow cells *ex vivo* in synthetic vascular grafts and then implanted in dogs induced capillary growth in the grafts. Thus, the bone marrow was explicitly put in the site where treatment was desired. Accordingly, Noishiki, et al., provides no teaching or suggestion that would motivate the skilled artisan to isolate endothelial progenitor cells from the bone marrow and use such isolated cells in the treatment of ischemia. It would actually teach away from that-suggesting transplantation of **whole** bone marrow directly **at the site of treatment**.

The secondary references do not make up for the deficiency of the primary references.

The Fenney, et al., Schnuerch, et al. and Yamaguchi, et al. references merely teach that endothelial progenitor cells express the CD34, TIE-2, FLK-1 markers.

Shi, et al. teaches that endothelialization of synthetic Dacron vascular grafts can arise from cells in circulation. Shi does not teach, nor would suggest, isolating endothelial progenitor cells and administering those cells for the treatment of ischemic tissue or treatment of an injured blood vessel. In fact, Shi by teaching that endothelialization can arise from cells in circulation would actually **teach away from** the present invention. If endothelialization can arise for cells in circulation as taught by Shi, the skilled artisan would have no motivation to go through the time consuming steps of isolating and then readministering endothelial progenitor cells.

The Bikfalvi, et al. and Asahara, et al. references merely teach the use of angiogenic proteins to stimulate revascularization.

Thus, if anything the combination of references teaches direct seeding of whole bone marrow, not isolated progenitor cells, at the site to be treated.

In summary, none of the references cited by the Examiner teach or suggest Applicants' surprising discovery that isolated endothelial progenitors cells when administered to a host selectively migrate to sites of active angiogenesis or blood vessel injury and thus can be used in the treatment of ischemic tissue or in the treatment of an injured blood vessel. Furthermore, the secondary references do not make up for

the deficiencies of the primary references. In the secondary references, there is no suggestion that Wilson, et al. or Noishiki, et al. be modified as suggested by the Examiner. In the absence of such a suggestion, combining references is not a proper basis for rejection under §103. Accordingly, *prima facie* obviousness has not been established, and one of ordinary skill in the art would not have been led to the present invention by the combined teachings of the cited references. As a result, the rejection under §103 should be withdrawn.

For the reasons stated above, Applicants respectfully submit that all of the rejections set forth in the April 1, 1998 Office Action have been overcome and that the case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this application is earnestly solicited.

Respectfully submitted,

DIKE, BRONSTEIN, ROBERTS
& CUSHMAN, LLP

Date: 9/18/98

David S. Resnick
(Reg. No.: 34,235)
Attorney for Applicant
130 Water Street
Boston, MA 02109
(617) 523-3400

wp:116796